REMARKS

Applicants thank the Examiner for the courtesy of the interview on April 25, 2002, at the U.S.P.T.O., between the Examiner, Drs. Bradley and Swindell, and Applicants' attorney Edward Gates. Claims 1, 17, 33, 57, 70, 97, and 110, have been amended to more particularly point out and distinctly claim the invention. The amendments are consistent with and are intended to effect the helpful suggestions offered by the Examiner at the interview after consideration of the additional supporting data provided by Drs. Bradley and Swindell (provided also herewith in the form of a Declaration from Dr. Bradley under 37 C.F.R. §1.132). It is believed that the claims as amended distinguish over the art and meet 35 U.S.C. §103 in all respects.

Claims 1, 5, 7-10, 12, 15, 17, 21, 23-26, 28, 31, 33, 37, 39-42, 46, 57, 62, 65, 69-70, 75, 78, 82, 84, 89-90, 94, 97, 101, 103, 107-108, 110 and 114, were pending prior to this Amendment.

Claims 119-187 are added herewith. These claims correspond to original claims 4, 6, 11, 13, 14, 16, 20, 22, 29, 30, 32, 36, 38, 43-45, 47-56, 58-61, 63, 64, 66-68, 71-74, 76, 77, 79-81, 83, 85-88, 91-93, 95, 96, 98-100, 102, 104-106, 109, 111-113, 115-118, respectively, which were canceled in the Preliminary and/or subsequent Amendments. No new matter has been added.

New claim 136 is original claim 48 which has been amended to include the limitation that "the fatty acid-anticancer compound conjugate is in an amount which is at least about 30% on a molar basis greater than the maximum tolerated dose (MTD) in the subject for the non-conjugated anticancer compound." No new matter has been added.

Claims 1, 5, 7-10, 12, 15, 17, 21, 23-26, 28, 31, 33, 37, 39-42, 46, 57, 62, 65, 69-70, 75, 78, 82, 84, 89-90, 94, 97, 101, 103, 107-108, 110 and 114 stand rejected under 35 U.S.C. §103(a) as being unpatentable over claims 1-6 of U.S. Patent No. 5,919,815 to Bradley et al.. According to the Examiner, the pending claims are unpatentable over claims 1-6 of U.S. Patent No. 5,919,815 under the judicially created doctrine of obviousness-type double patenting.

Claims 1, 17, and 33, as amended, more particularly point out and distinctly claim Applicants' unexpected discovery that higher concentrations of anticancer drugs can be delivered to subjects, in amounts never before expected. The dose-limiting toxicity of the anticancer drug is altered due to its conjugation to a fatty acid. As presented to the Examiner during the interview, and as reiterated herewith

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and in the accompanying Declaration by Applicants, it is Applicants' unexpected discovery that concentrations of fatty acid-anticancer drug conjugate as little as 30% (on a molar basis) greater than the maximum tolerated dose (MTD) for the unconjugated anticancer drug in the subject are curative notwithstanding that toxicities and volumes of distributions are disproportionately affected to a much greater extent.

It is Applicants' belief that by reading the '815 patent, one of ordinary skill in the art would not have predicted that: (i) higher concentrations of anticancer drugs (i.e., concentrations higher than a drug's MTD) can be delivered to subjects, and/or (ii) concentrations of fatty acid-anticancer drug conjugate as little as 30% (on a molar basis) greater than the maximum tolerated dose (MTD) for the unconjugated anticancer drug in the subject can be curative.

Applicants submit herewith a Declaration by Dr. Matthews Bradley under 37 CFR §1.132 describing experiments previously performed by Applicants that compare the *in vivo* effects of anticancer agents and anticancer agent-fatty acid conjugates on tumors, in an effort by Applicants to understand the unexpected findings of the present invention. The Declaration describes experiments that examined the antitumor properties, dosage toxicity, and pharmacokinetic properties of anticancer drugs and of their fatty acid conjugates.

In these experiments, Applicants confirmed that DHA-paclitaxel possesses increased antitumor activity relative to paclitaxel, and can be given at 4.4 times the paclitaxel MTD (in molar terms) (i.e., it is less toxic than paclitaxel). Applicants also showed that the lowest MTD increase for DHA-paclitaxel that results in an improved cure rate relative to paclitaxel is about 30%. In addition, Applicants demonstrated that the uptake of DHA-paclitaxel in tumors is higher than that of paclitaxel, and that the time the paclitaxel concentration in tumors is above the minimum therapeutic concentration required to halt tumor growth is 10-times longer following DHA-paclitaxel administration than following paclitaxel administration.

In human clinical trials Applicants confirmed all of their previous findings using animal models and further showed, unexpectedly, the reduced toxicity associated with the administration of the DHA-paclitaxel conjugate. For example, even at the safely administered dosage that is 3.3-5.9 times (on a molar basis) the paclitaxel MTD, DHA-paclitaxel hypersensitivity reactions occur at 16% of the rate observed for paclitaxel, hair loss (alopecia) occurs at 5% of the rate observed for paclitaxel, nerve toxicity (peripheral neuropathy) occurs at 38% of the rate observed for paclitaxel, and damage to the mucus

membranes of the body (stomatitis/mucositis) occurs at 51% of the rate observed for paclitaxel. Please also see Exhibits A and B (Applicants' published manuscripts relating to the foregoing).

Overall, Applicants observations in these experiments further explained the unexpected finding of increased antitumor efficacy of the anticancer drug-fatty acid conjugate relative to the anticancer drug, and further showed the unexpected findings of "reduced toxicities" associated with the administration of such conjugates relative to the anticancer drug.

The foregoing unexpected results are embraced by the claims as amended herewith. No new matter has been added. For example, method claims 17, 21, 23, and 28 describe administering fatty acid-anticancer compound conjugates in amounts which far exceed the maximum tolerated dose for the unconjugated anticancer compounds, amounts that have also been associated with an improved cure rate. Claim 33 describes a kit for carrying out the method of claim 17. Claim 1 describes a formulation in a container for administration to a subject, wherein the container contains the amount of conjugate necessary for carrying out the method described in claim 17.

As argued previously by Applicants, these compositions were not remotely suggested and were unpredictable from the '815 patent.

In summary, the dose ranges and formulations and compositions claimed in the instant application are neither shown nor suggested by the prior art. For example, it simply is unpredictable from the prior art that one could administer a fatty acid-anticancer drug conjugate in an amount at least about 30% (on a molar basis) greater than the maximum tolerated dose (MTD) in a subject for the unconjugated anticancer drug and see an improved cure rate.

Applicants re-iterate Applicants' arguments filed in the previous responses and respectfully request reconsideration and withdrawal of the rejections, particularly in view of the amendments to the claims, which are intended to clarify that according to the present invention one could administer a fatty acid-anticancer drug conjugate in an amount at least about 30% (on a molar basis) greater than the maximum tolerated dose (MTD) in a subject for the unconjugated anticancer drug and see an improved cure rate. These are unexpected findings over and above the teachings of the cited '815 patent.

It is believed that all the claims as amended are in condition for allowance. If the Examiner does not believe that the present response is adequate to distinguish the claims over the cited reference, then Applicants request the opportunity to discuss the issues in a further interview with the Examiner in order to advance prosecution.

Respectfully submitted,

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MARKED-UP CLAIMS

1. (Twice Amended) A fatty acid-anticancer compound conjugate composition for administration to a subject, comprising at least one fatty acid-anticancer compound conjugate in a container for administration to a subject, wherein the amount of the fatty acid-anticancer compound in the container is at least about [10]30% on a molar basis greater than the maximum tolerated dose (MTD) in the subject for the unconjugated at least one anticancer compound, wherein the container is a container for intravenous administration.

17. (Twice Amended) A method for treating a subject having an abnormal mammalian cell proliferative disorder, comprising administering to the subject a fatty acid-anticancer compound conjugate composition in an amount which is at least about [10]30% on a molar basis greater than the maximum tolerated dose (MTD) in the subject for the unconjugated at least one anticancer compound.

33. (Twice Amended) A kit for administration of a fatty acid-anticancer compound conjugate composition to a subject, comprising

a container containing at least one fatty acid-anticancer compound conjugate, and

instructions for administering the at least one fatty acid-anticancer compound conjugate to subject in need of such treatment in an amount which is at least about [10]30% on a molar basis greater than the maximum tolerated dose (MTD) in the subject for the unconjugated at least one anticancer compound.